

correlated with the presence of an autoimmune disease associated with a reduction in NF $\kappa$ B activity.

70. The method of claim 65, wherein said reduction in said proteolytic products is determined by measuring the level of said proteolytic products in the nucleus of the cell.

71. The method of claim 65, wherein said reduction in said proteolytic products is determined by measuring the level of said proteolytic products in the cytoplasm of the cell.

#### REMARKS

Claims 65-71 are pending. Claims 65, 70 and 71 are amended herein.

#### Rejection of Claims 65-71 under 35 U.S.C. §112, first paragraph

Claims 65-71 are rejected under 35 U.S.C. §112, first paragraph for alleged failure to comply with the written description requirement.

The Examiner states that there is “no support for the phrase ‘wherein a reduction in the level of NF $\kappa$ B proteolytic products’ as recited in claim 65.

Applicants have amended claim 65 and dependent claims 66-71 to replace the phrase “NF $\kappa$ B proteolytic products” with the phrase “proteolytic products derived from the proteolytic processing of NF $\kappa$ B by said proteasomes”.

Applicants submit that support for the phrase “proteolytic products derived from the proteolytic processing of NF $\kappa$ B by said proteasomes” is found in the specification at p. 10, lines 10-20 wherein it is stated,

“[a]s used herein in reference to proteasome activity, the term ‘reduction’ refers to the failure of the proteasome to cleave a target ubiquitinated protein at as few as one-, more than one-, or even as many as all of the sites that it normally (i.e., in a genetically wild-type or otherwise healthy individual) recognizes and cleaves in that protein. Preferably such a reduction involves failure to cleave the target protein at 5-10% of sites, more preferably at 20-50% of sites, and most preferably at 75-100% of such sites.”

The specification teaches the formation of proteolytic products derived from the proteolytic processing of NF $\kappa$ B by a proteasome at p. 11, lines 14-16, wherein it is stated,

“preferably, the reduction in proteasome activity comprises a reduction of proteolytic processing of NF $\kappa$ B or a subunit thereof.”

It is also stated at p. 42, line 28- p. 43, line 2, “[t]he kinase, in turn, phosphorylates the NF $\kappa$ B inhibitor protein I $\kappa$ B marking it for ubiquitination. In unstimulated cells, I $\kappa$ B binds to- and inhibits the activity of NF $\kappa$ B. When ubiquitinated I $\kappa$ B is degraded by the proteasome, NF $\kappa$ B translocates to the nucleus where it activates transcription.”

Applicants also submit that as of the filing date of the instant application it was known in the art that NF $\kappa$ B is proteolytically processed via the proteasome pathway (see Palombella et al., 1994, Cell, 78: 773-85 (Exhibit A; Chen et al., 1995, Genes Dev., 9:1586-97 (Exhibit B); Li et al., 1995, Biochem. Biophys. Res. Commun., 215:292-301 (Exhibit C)).

In view of the above, Applicants submit that the specification clearly provides support for a “method of screening for autoimmune disease associated with a reduction in NF $\kappa$ B activity in a mammal deemed to be at risk for an autoimmune disease, comprising: a) providing a biological sample from a mammal; and b) detecting activity of proteasomes in said sample by measuring the level of **proteolytic products derived from the proteolytic processing of NF $\kappa$ B by said proteasomes** generated by said proteasomes, wherein a reduction in the level of said proteolytic products from a basal state is correlated with the presence of an autoimmune disease associated with a reduction in NF $\kappa$ B activity, as claimed in amended claim 65 and dependent claims 66-71.

In view of the above, Applicants respectfully request withdrawal of the 35 U.S.C. §112, first paragraph rejection of claims 65-71.

Rejection of claims 65-71 under 35 U.S.C. §112, second paragraph

Claims 65-71 are rejected under 35 U.S.C. §112, second paragraph for alleged indefiniteness.

The Examiner states, “[i]n claims 65, 70 and 71, the phrase “NF $\kappa$ B proteolytic products is repugnant to the art recognized function of NF $\kappa$ B, because NF $\kappa$ B is not recognized to enzymatically cleave proteins”.

Applicants have amended claim 65 and dependent claims 66-71 to replace the phrase “NF $\kappa$ B proteolytic products” with the phrase “proteolytic products derived from the proteolytic

processing of NF $\kappa$ B by said proteasomes". Support for this amendment is discussed above in Applicants response to the 35 U.S.C. §112, first paragraph rejection of claims 65-71.

In view of the above, Applicants submit that the phrase "proteolytic products derived from the proteolytic processing of NF $\kappa$ B by said proteasomes" is not indefinite and respectfully requests withdrawal of the 35 U.S.C. §112, second paragraph rejection of claims 65-71.

Applicants submit that in view of the foregoing amendments and remarks, all issues relevant to patentability raised in the outstanding Office Action have been addressed. Applicants respectfully request reconsideration of the claims.

Respectfully submitted,

Date:

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Name: Kathleen M. Williams  
Registration No.: 34,380  
Palmer & Dodge LLP  
One Beacon Street  
Boston, MA 02108  
Tel: 617-573-0100

**Marked-up sheet for claim amendment**

65. (Amended) A method of screening for autoimmune disease associated with a reduction in NF $\kappa$ B activity in a mammal deemed to be at risk for an autoimmune disease, comprising:

- a) providing a biological sample from a mammal; and
- b) detecting activity of proteasomes in said sample by measuring the level of proteolytic products derived from the proteolytic processing of NF $\kappa$ B by said proteasomes [proteolytic products] generated by said proteasomes, wherein a reduction in the level of [NF $\kappa$ B] said proteolytic products from a basal state is correlated with the presence of an autoimmune disease associated with a reduction in NF $\kappa$ B activity.

70. (Amended) The method of claim 65, wherein said reduction in [NF $\kappa$ B] said proteolytic products is determined by measuring the level of [NF $\kappa$ B] said proteolytic products in the nucleus of the cell.

71. (Amended) The method of claim 65, wherein said reduction in [NF $\kappa$ B] said proteolytic products is determined by measuring the level of [NF $\kappa$ B] said proteolytic products in the cytoplasm of the cell.